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(54)【発明の名称】　血液浄化用中空糸膜および中空糸膜型人工腎臓

(57)【要約】
【課題】　本発明は、外表面へエンドトキシンを吸着する血液浄化用中空糸膜および中空糸膜型人工腎臓を提供すること、また、中空糸膜中の親水性高分子が少なくかつ血小板を吸着させない血液浄化用中空糸膜および中空糸膜型人工腎臓を提供すること。
【解決手段】　親水性高分子と疎水性高分子をその共通溶媒に溶解混合させた製膜原液から製造された中空糸膜において、該中空糸膜の外表面における該疎水性高分子に対する親水性高分子の比率が５～２５％である血液浄化用中空糸膜である。

【特許請求の範囲】
【請求項１】　親水性高分子と疎水性高分子をその共通溶媒に溶解混合させた製膜原液から製造された中空糸膜において、該中空糸膜の外表面における疎水性高分子に対する親水性高分子の比率が５～２５％であることを特徴とする血液浄化用中空糸膜。
【請求項２】　前記疎水性高分子がポリスルホン系樹脂であることを特徴とする請求項１に記載の血液浄化用中空糸膜。
【請求項３】　前記親水性高分子がポリビニルピロリドン、ポリエチレングリコール及びその共重合体、ポリプロピレングリコールおよびその共重合体からなる群から選ばれたものであることを特徴とする請求項１または２に記載の血液浄化用中空糸膜。
【請求項４】　前記中空糸膜の内表面に抗血栓性物質がコーティングされていることを特徴とする請求項１ないし３に記載の血液浄化用中空糸膜。
【請求項５】　前記抗血栓性物質がビタミンＥであることを特徴とする請求項１ないし４に記載の血液浄化用中空糸膜。
【請求項６】請求項１ないし５に記載された中空糸膜を有する中空糸膜型人工腎臓。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、血液浄化療法、特に血液透析療法及び血液濾過透析療法に用いる血液浄化用中空糸膜および中空糸膜型人工腎臓に関する。より詳しくは、透析液側からのエンドトキシンの侵入を防ぐ一方、血液接触面においては血小板の吸着を抑えた血液浄化用中空糸膜および中空糸膜型人工腎臓に関する。
【０００２】
【従来の技術】腎不全治療のために、現在中空糸膜を用いた種々の人工腎臓が用いられている。近年、β２－ミクログロブリンを一つの指標とした分子量１万以上の低分子量タンパク質の除去が、治療に有効であることが示され、低分子量タンパク質が通過できる微孔を有する血液浄化膜の開発が盛んに行われてきている。さらに、積極的に低分子量タンパク質の除去を行うために、血液透析と血液濾過を組み合わせた同時血液濾過透析療法が行われている。
【０００３】しかしながら、上記の治療の際、膜を挟んで反対側を流れる透析液が血液側へ流入するので、低分子量タンパク質を除去するために膜の微孔の大きさ（ポアサイズ）を拡大していくと、透析液に含まれるエンドトキシン（内毒素）が血液側へ侵入する可能性が高まり、発熱等の副作用を惹起することが懸念されている。
【０００４】エンドトキシンは、疎水性部分を有し、疎水性材料へ吸着しやすいことが知られており、この原理を利用したエンドトキシン除去フィルターが開発されている。特開平１０－１５１１９６号、特開平１０－１１８４７２号は、疎水性高分子のみから中空糸膜を作製し、エンドトキシンを吸着させている。さらに疎水性高分子が血液中のタンパク質を吸着しやすいことによる透水性能の低下を改善させるために中空糸内面のみに親水性高分子を付着させている。これらの出願においては、製膜原液に親水性高分子が存在すると膜外表面の疎水化は不可能であるとして、製膜原液に親水性高分子を混合させず、製膜後に内表面を親水化処理している。
【０００５】従来の技術では、疎水性高分子からなる中空糸膜に親水性高分子を付与することによって、透水性能が改善することと、中空糸膜の親水性が増加することによるエンドトキシンの吸着能力の低下との調整をとりながら適切な範囲を特定することは示されていなかった。
【０００６】また、疎水性高分子の製膜原液に親水性高分子を添加し製膜してから、洗浄等により外表面の親水性高分子の量を減少させた場合、血液と接触する表面の親水性高分子量も減少し、血小板の付着等が生じることが特開平６－２９６６８６号に記載されている。
【０００７】
【発明が解決しようとする課題】本発明の目的は、上記問題を解決した親水性高分子と疎水性高分子が混合された製膜原液から製膜された中空糸膜において、外表面へエンドトキシンを吸着する血液浄化用中空糸膜および中空糸膜型人工腎臓を提供することにある。
【０００８】さらに本発明の目的は、中空糸膜中の親水性高分子が少なくかつ血小板を吸着させない血液浄化用中空糸膜および中空糸膜型人工腎臓を提供することにある。
【０００９】
【課題を解決するための手段】上記諸目的は、以下の本発明の血液浄化用中空糸膜および中空糸膜型人工腎臓により達成される。
【００１０】（１）　親水性高分子と疎水性高分子をその共通溶媒に溶解混合させた製膜原液から製造された中空糸膜において、該中空糸膜の外表面における疎水性高分子に対する親水性高分子の比率が５～２５％であることを特徴とする血液浄化用中空糸膜。
【００１１】（２）　前記疎水性高分子がポリスルホン系樹脂であることを特徴とする（１）に記載の血液浄化用中空糸膜。
【００１２】（３）　前記親水性高分子がポリビニルピロリドン、ポリエチレングリコール及びその共重合体、ポリプロピレングリコールおよびその共重合体からなる群から選ばれたものであることを特徴とする（１）または（２）に記載の血液浄化用中空糸膜。
【００１３】（４）　前記中空糸膜の内表面に抗血栓性物質がコーティングされていることを特徴とする請求項（１）ないし（３）に記載の血液浄化用中空糸膜。
【００１４】（５）　前記抗血栓性物質がビタミンＥで

あることを特徴とする（１）ないし（４）に記載の血液浄化用中空糸膜。

【００１５】（６）上記（１）ないし（５）に記載された中空糸膜を有する中空糸膜型人工腎臓。

【００１６】

【発明の実施の形態】以下本発明を詳細に説明する。

【００１７】本発明の血液浄化用中空糸膜を形成する疎水性高分子は、ポリメチルメタクリレート、ポリスチレン、ポリスルホン、セルローストリアセテート、ポリカーボネート、ポリアリレート等が挙げられ、これらの単独、または２種以上を組み合わせて使用してもよい。これらの疎水性高分子は、エンドトキシン吸着性を有し、人工腎臓として用いた場合に、透析液側からのエンドトキシンの血液側への侵入を防止することができる。

【００１８】本発明の血液浄化用中空糸膜は、その製膜原液に親水性高分子を含み、製膜後、一定の洗浄処理を受け、中空糸膜に残存する。本発明に用いられる親水性高分子は、ポリビニルアルコール、ポリエチレングリコール、ポリプロピレングリコール、ポリビニルピロリドン、ポリテトラメチレンオキサイド等の重合体又はこれらを含む共重合体を含む。好ましくは製膜性、孔径制御の容易さの点でポリビニルピロリドンが好ましい。また、好ましい重量平均分子量は、１万から５百万ダルトン、より好ましくは３万から２百万ダルトンである。透析膜として機能させるための孔径制御が容易である。

【００１９】本発明の血液浄化用中空糸膜に残存する透析液側（通常、中空糸膜の外表面）の親水性高分子の疎水性高分子に対する比率は、５から２５％が好ましい。この範囲であれば、透析液中に含まれるエンドトキシンを有効に吸着させることができる。より好ましくは５から２０％である。透析液側の親水性高分子の疎水性高分子に対する比率は、Ｘ線光電子分光法（Ｘ－ｒａｙ　ｐｈｏｔｏｅｌｅｃｔｒｏｎ　ｓｐｅｃｔｒｏｓｃｏｐｙ，ＸＰＳ）、赤外線分光法、核磁気共鳴法等の測定方法により測定した、該親水性高分子と該疎水性高分子の存在比率をいう。例えば、疎水性高分子としてポリスルホン樹脂（ＰＳ）、親水性高分子としてポリビニルピロリドン（ＰＶＰ）を選択した場合、ＸＰＳにより、特徴的な元素であるイオウ（ＰＳ）と窒素（ＰＶＰ）の元素比とＰＳおよびＰＶＰの繰り返し単位分子量とから、中空糸膜表面に存在するＰＳとＰＶＰそれぞれの総原子量の比率を算出し求めることができる。

【００２０】また、本発明の中空糸膜全体の疎水性高分子に対する親水性高分子の比率は、１．０から６．０重量％が好ましい。より好ましくは２．０から５．０重量％である。下限値以下では、洗浄操作を過剰に行わなければならず、効率が悪い。また、上限値以上では、中空糸膜外表面から膜内部へ向かって急激に親水性高分子の比率が上昇することとなり、エンドトキシンの吸着する領域が少なくなり好ましくない。中空糸膜全体の親水性高分子の比率は、中空糸膜を溶媒に溶解してＮＭＲ等により分析する方法や、元素分析による方法等がある。例えば、疎水性高分子としてポリスルホン、親水性高分子としてポリビニルピロリドンを用いた場合、元素分析による窒素とイオウの元素比と各高分子の繰り返し単位の分子量とから、重量比を求めることができる。

【００２１】中空糸膜を製膜する場合、従来より用いられている湿式紡糸方法あるいは乾湿式紡糸方法が使用できる。これらの紡糸方法を行う場合、前記疎水性高分子と親水性高分子をこれらの共通溶媒に溶解し製膜原液を調整する。この共通溶媒としては、Ｎ，Ｎ－ジメチルアセトアミド、Ｎ，Ｎ－ジメチルホルムアミド、Ｎ－メチルピロリドン、ジメチルスルフォキシド等の溶媒が溶解性が高く好適であるが、これらに限定されるものではなく、また、２種以上の溶媒を混合して用いてもよい。好ましくは入手の容易さの点で、Ｎ，Ｎ－ジメチルアセトアミド、Ｎ，Ｎ－ジメチルホルムアミドを単独で用いる。

【００２２】また、製膜原液に粘度調節や孔径制御等の微調整を行うために、アルコール、グリセリン、水等を適量添加しても構わない。排液処理の点から水が好ましく、製膜原液中で０．１から５重量％が上記微調整に好ましい。

【００２３】製膜原液中の疎水性高分子の濃度は、低すぎると膜強度が小さく、紡糸作業、組立作業を慎重に行わなければならず、効率が悪い。また、濃度が高すぎると製膜原液の粘度が上昇し、膜が緻密となり、人工腎臓としての必要な孔径得るための条件設定が難しい。疎水性高分子としてポリスルホンを用いた場合、好ましい疎水性高分子の製膜原液中の濃度は、１０から３０重量％、好ましくは１２から２５重量％、さらに好ましくは１５から１９重量％である。詳細には、疎水性高分子の種類、分子量等により好ましい濃度範囲が変動するため、この範囲に限定されるものではない。

【００２４】製膜原液中の親水性高分子の濃度は、低すぎると良好な孔径制御が困難となり、高すぎると製膜原液の粘度が上昇し、紡糸性が悪化する。親水性高分子として重量平均分子量４．５万ダルトンのポリビニルピロリドンを用いた場合、好ましい製膜原液中の濃度は、５から１５重量％、より好ましくは７から１０重量％である。分子量が高いものを用いた場合は、低い濃度でもよく、分子量が低いものを用いた場合は、高い濃度が好ましい。

【００２５】湿式紡糸あるいは乾湿式紡糸の際、２重管ノズルの内管より吐出する内部液としては、上記共通溶媒と水との混合物が主として用いられる。製膜原液の凝固速度の制御のために上記共通溶媒を２種以上混合したものや、他の液体を混合してもよい。

【００２６】２重管ノズルより吐出された製膜原液は、水を主体とした凝固浴に浸漬される。製膜原液は、凝固

浴によって、中空糸膜としてしっかり形づけられる。その後、必要に応じ水洗浴に浸漬され水洗される。水洗浴の温度が高いほど、外表面のＰＶＰが洗浄される。中空糸膜の外表面のＰＶＰを好ましい比率に調節するために、水洗浴の温度を４０から８０℃とすることが好ましい。特に５０から７０℃で洗浄することが好ましい。該水洗浴の洗浄水は、中空糸膜の周囲を移動しているほうが洗浄効率が高いため、洗浄水を循環させて用いても良い。この際、循環中に洗浄水中のＰＶＰ濃度が徐々に高くなり洗浄効率が低下してくるので、常に新たな洗浄水を供給することが好ましい。１時間に供給する新たな洗浄水の量が、洗浄水総量の１０から５０％であることが好ましい。

【００２７】水洗浴で洗浄された中空糸膜は巻き取りが行われ、さらに温水、アルコール、アルコールと水との混合溶液等で洗浄することにより中空糸膜外表面のＰＶＰを積極的に洗浄することが可能である。このようにして得られた中空糸膜の外表面の親水性高分子の存在比率を５から２５％、好ましくは５から２０％とすることにより、外表面へのエンドトキシン吸着能が得られる。親水性高分子の外表面存在比率が５％未満であると、水透過性が減少する。親水性高分子の外表面存在比率が２５％を越えると外表面の親水性が高くなり、エンドトキシンの吸着能が低下する。

【００２８】また、本発明の血液浄化用中空糸膜は、血液と接触する中空糸内表面の血小板付着を抑制するため、抗血栓性物質を付与することが好ましい。中空糸膜外表面の親水性高分子の存在比率を５から２５％とした場合、内表面の親水性高分子の存在比率も低下し、血小板が付着しやすくなるからである。抗血栓性物質とはスチレン－ヒドロキシエチルメタクリレート共重合体、親水基を有する（メタ）アクリル酸系モノマーと疎水基を有する（メタ）アクリル酸系モノマーとの重合体のような親水性部分と疎水性部分を有する高分子物質、エイコサペンタエン酸やドコサヘキサエン酸等の長鎖不飽和脂肪酸、ビタミンＥ等の脂溶性ビタミン類などが挙げられる。処理の容易さや熱に対する安定性が高い点からビタミンＥが好ましい。ビタミンＥとしてはα－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－酢酸トコフェロール、α－ニコチン酸トコフェロールなどが挙げられる。

【００２９】（実施例１）ポリスルホン（Ｐ－１７００）１９重量%、ポリビニルピロリドン（Ｋ－３０）９重量%、Ｎ，Ｎ－ジメチルホルムアミド７２重量%を均一溶解させ製膜原液を調整した。内部液はＮ，Ｎ－ジメチルホルムアミド６０重量%、水４０重量%の混合液を用いた。

【００３０】上記の製膜原液と内部液をそれぞれ２重管吐出ノズルの外管および内管から同時に空気中に吐出し、水が満たされた凝固浴を通過させた。凝固浴を通過させた後、６０℃の温水を１Ｌ／分で１時間シャワー洗浄した。

【００３１】シャワー洗浄後、中空糸膜を巻き取り１万本の束にし、さらに１１０℃１時間水中で処理し、洗浄した。

【００３２】（実施例２）ポリスルホン（Ｐ－１７００）１９重量%、ポリビニルピロリドン（Ｋ－３０）９重量%、Ｎ，Ｎ－ジメチルホルムアミド７２重量%を均一溶解させ製膜原液を調整した。内部液は、Ｎ，Ｎ－ジメチルホルムアミド６０重量%、水４０重量%の混合液に対して０．１重量%のα－酢酸トコフェロールと０．１重量%のポリエチレングリコール－ポリプロピレングリコール共重合体（プルロニックＦ－６８、旭電化工業社製）を添加して用いた。

【００３３】上記の製膜原液と内部液をそれぞれ２重管吐出ノズルの外管および内管から同時に空気中に吐出し、水が満たされた凝固浴を通過させた。凝固浴を通過させた後、６０℃の温水を１Ｌ／分で１時間シャワー洗浄した。

【００３４】シャワー洗浄後、中空糸膜を巻き取り１万本の束にし、さらに１１０℃１時間水中で処理し、洗浄した。

【００３５】（比較例１）ポリスルホン（Ｐ－１７００）１９重量%、ポリビニルピロリドン（Ｋ－３０）９重量%、Ｎ，Ｎ－ジメチルホルムアミド７２重量%を均一溶解させ製膜原液を調整した。内部液は、Ｎ，Ｎ－ジメチルホルムアミド６０重量%、水４０重量%の混合液して用いた。

【００３６】上記の製膜原液と内部液をそれぞれ２重管吐出ノズルの外管および内管から同時に空気中に吐出し、水が満たされた凝固浴を通過させた。凝固浴を通過させた後、６０℃の温水を１Ｌ／分で１０分間シャワー洗浄した。

【００３７】（比較例２）ポリスルホン（Ｐ－１７００）１９重量%、ポリビニルピロリドン（Ｋ－３０）１重量%、Ｎ，Ｎ－ジメチルホルムアミド８０重量%を均一溶解させ製膜原液を調整した。内部液は、Ｎ，Ｎ－ジメチルホルムアミド６０重量%、水４０重量%の混合液して用いた。

【００３８】上記の製膜原液と内部液をそれぞれ２重管吐出ノズルの外管および内管から同時に空気中に吐出し、水が満たされた凝固浴を通過させた。凝固浴を通過させた後、６０℃の温水を１Ｌ／分で１時間シャワー洗浄した。

【００３９】シャワー洗浄後、中空糸膜を巻き取り１万本の束にし、さらに１１０℃１時間水中で処理し、洗浄した。

【００４０】実施例１、２、比較例１、２で得られた中空糸膜の外表面のポリビニルピロリドンの存在比率をＸＰＳにより測定し、さらに、中空糸膜の内側と連通する

血液入口と血液出口、および中空糸膜の外面側と連通する透析液入口と透析液出口とを有するハウジングを用いて有効膜面積１．５m^2の中空糸膜型人工腎臓を作製し、透水性能とエンドトキシン吸着能を測定した。測定結果を表１に示す。

【００４１】透水性能の測定は、上記中空糸膜型人工腎臓を用いて、逆浸透水を中空糸膜の内側に流速２００ｍｌ／ｍｉｎで送水し、中空糸膜の外面より流速１５ｍｌ／ｍｉｎで濾過し、その時の膜間圧力差を測定して算出した。

【００４２】エンドトキシンの吸着能の測定は、上記中空糸膜型人工腎臓を用いて以下の通り行った。エンドトキシン濃度８００ＥＵ／Ｌの透析液を、透析液入口より流速３０ｍｌ／ｍｉｎで送液し、透析液出口からの流出量をポンプを用いて５ｍｌ／ｍｉｎに制御し、積極的に中空糸膜の外面側から内側へエンドトキシンを含有する透析液の濾過を４時間行い、中空糸膜の外側から中空糸膜の内側へ濾過された透析液を貯留し、該貯留液のエンドトキシン濃度を測定した。試験液は再循環せず、一方向にのみ流通した。

【００４３】

【表１】

	膜全体のＰＶＰ比率（%）	ＰＶＰ外表面比率（%）	透水性能（ml/mmHg･hr）	エンドトキシン濃度（ＥＵ／Ｌ）
実施例１	２．８	１７	４９０	検出限界以下
実施例２	２．３	１４	４７０	検出限界以下
比較例１	６．７	３０	４６０	８
比較例２	０．８	３	２０	検出限界以下

検出限界：１ＥＵ／Ｌ

【００４４】表１の通り、実施例１、２は、比較例１と同等の透水性能を有し、かつ、エンドトキシンの吸着能を有している。一方、比較例１は、４時間の透析液の逆濾過により、血液側へエンドトキシンが検出された。また、比較例２は、血液側のエンドトキシンは検出されなかったが、透水性能が著名に減少した。

【００４５】（実施例３）ヒドロキシエチルメタクリレート、メチルメタクリレートおよびブチルメタクリレートのランダム共重合体（ポリマー１）とポリパーフルオロアルキルメタクリレート（ポリマー２）のブロック共重合体（ポリマー１と２の比率は重量比５０：５０、平均分子量３５，０００）のポリマー濃度３０％メチルイソブチルケトン溶液をメタノールでポリマー濃度を０．７％に希釈した。この溶液を実施例１のPS膜内面に通液した後５０℃の乾燥にて溶媒を除去し、ポリマーをPS膜上にコーティングした。

【００４６】得られた中空糸膜で有効膜面積１．５m^2の人工腎臓の透水性能は３２０ｍｌ／ｍｍＨｇ・ｈｒであった。

【００４７】（血小板数の経時変化）実施例１、実施例２および実施例３で得られた中空糸膜を用いて膜面積３００cm^2のミニモジュールを作製した。

【００４８】家兎（体重２．７～３．３ｋｇ）を用い、ネンブタール生食２倍希釈液１ｍｌ／ｋｇを静注して麻酔した。固定台に家兎を固定し頸動静脈の血管を確保し、回路及びミニモジュールを接続して血流量ＱＢ＝１０ｍｌ／ｍｉｎで抗凝固剤を用いずに２時間循環した。採血は、ミニモジュールの動脈側採血ポートから行い、血小板数の経時変化を測定した。なお、血小板の変化率はヘマトクリット値にて補正した（下式）。

【００４９】

【数１】

$$\text{血球変化率} = \frac{PL_t \times Ht_0}{PL_0 \times Ht_t} \times 100\%$$

PL_c：循環前の血球数、Ht_0：循環前のヘマトクリット値

PL_t：循環ｔ時間の血球数、Ht_t：循環ｔ時間のヘマトクリット値

【００５０】結果を表２に示す。

【００５１】

【表２】

時間(分)	実施例１	実施例２	実施例３
０	100	100	100
５	90.1	93.5	89.7
１０	89.1	90.8	86.0
１５	83.8	90.4	84.6
２０	81.9	87.2	85.7
２５	79.9	86.7	84.3
３０	75.1	85.5	84.9
４５	65.5	84.0	83.3
６０	61.6	80.9	81.6
１２０	57.5	84.8	81.3

【００５２】（赤血球膜MDAの測定）膜面積６００ｃｍ^{2}の実施例１、実施例２のミニモジュールを用いて、以下の操作を行った。

【００５３】まず、滅菌済みミニモジュールを５０ｍｌ生食でプライミングし、１０Ｕ／ｍｌヘパリン加血をミニモジュールに充填して３７℃で６時間インキュベートした。その後、ミニモジュールから血液を回収し、血球計算機（Ｓｙｓｍｅｘ　ＳＥ９０００、東亜医用電子株式会社）により赤血球数をカウント（血算）した。また、ミニモジュールから回収した血液１．８ｍｌ（血算済み）を血漿分離（３，０００ｒｐｍ、１５ｍｉｎ、４℃）により血漿を除去し、１０ｍＭ ＰＢＳ（ｐＨ８．０）５．４ｍｌに沈殿した赤血球を懸濁させ、遠心分離（３，０００ｒｐｍ、１５ｍｉｎ、４℃）し、上清のＰＢＳを除去して洗浄した。この洗浄操作を合計３回行った後、上清のＰＢＳを除去し、５ｍＭＰＢＳ（ｐＨ８．０）５．４ｍｌを添加し、赤血球を溶血させた。

【００５４】上記溶血させた試料を遠心分離（１０，０００ｒｐｍ、１５ｍｉｎ、４℃)して、上清のＰＢＳを除去し２．５ｍＭＰＢＳ（ｐＨ８．０）５．４ｍｌを赤血球に混合し溶血させる。さらに遠心分離（１０，０００ｒｐｍ、１５ｍｉｎ、４℃)して、上清のＰＢＳを除去し１．２５ｍＭＰＢＳ（ｐＨ８．０）５．４ｍｌを赤血球に混合し溶血させ、遠心分離（１０，０００ｒｐｍ、１５ｍｉｎ、４℃)した。１．２５ｍＭＰＢＳでの溶血、遠心分離、洗浄操作を合計５回繰り返す。最後に上清のＰＢＳを除去した後、１．２５ｍＭＰＢＳで全量を２mlに合わせた。

【００５５】上記の調整法によって得られた赤血球膜を試料としてＴＢＡ法によりＭＤＡ（マロンジアルデヒド）を測定した（過酸化脂質テストワコー：和光純薬工業社製）。操作方法を以下に示す。

【００５６】結果を表３に示す。

【００５７】

【表３】

赤血球過酸化脂質（n=5）

	MDA nmol／10^{10}RBC
PRE	３．５０７
実施１	６．７０１
実施２	５．５５８

【００５８】中空糸膜内面側に抗血栓性物質をコーティングすることにより、血小板の減少を抑制することができることがわかる。また、ビタミンＥを用いた場合には赤血球膜脂質の過酸化を抑制できることがわかる。

【００５９】

【発明の効果】以上説明してきた通り、本発明は、親水性高分子と疎水性高分子が混合された製膜原液から製膜された中空糸膜において、外表面へエンドトキシンを吸着する血液浄化用中空糸膜および中空糸膜型人工腎臓を得ることができる。

【００６０】さらに本発明は、中空糸膜中の親水性高分子が少なくかつ血小板を吸着させない血液浄化用中空糸膜および中空糸膜型人工腎臓を得ることができる。

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(54) **HOLLOW FIBER MEMBRANE FOR HEMATOCATHARSIS AND HOLLOW FIBER MEMBRANE TYPE ARTIFICIAL KIDNEY**

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a hollow fiber membrane for hematocatharsis and a hollow fiber membrane type artificial kidney in which endotoxine is adsorbed on an outer surface and to provide a hollow fiber membrane for hematocatharsis and a hollow fiber membrane type artificial kidney in which a hydrophilic polymer in the hollow fiber membrane is less and a blood platelet is not adsorbed.
SOLUTION: In the hollow fiber membrane prepared from a membrane- forming stock solution in which a hydrophilic polymer and a hydrophobic polymer are solvent and mixed in a common solvent, a hollow fiber membrane for hematocatharsis in which a ratio of the hydrophilic polymer is used against the hydrophobic polymer on an outer surface of the hollow fiber membrane is 5-25%.

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CLAIMS

[Claim(s)]
[Claim 1] The hollow fiber for blood purification characterized by the ratio of the hydrophilic macromolecule to the hydrophobic macromolecule in the outside surface of this hollow fiber being 5 - 25% in the hollow fiber manufactured from the film production undiluted solution which made the common solvent carry out dissolution mixing of a hydrophilic macromolecule and the hydrophobic macromolecule.
[Claim 2] The hollow fiber for blood purification according to claim 1 characterized by said hydrophobic macromolecule being polysulfone system resin.
[Claim 3] The hollow fiber for blood purification according to claim 1 or 2 characterized by being chosen out of the group which said hydrophilic giant molecule becomes from a polyvinyl pyrrolidone, a polyethylene glycol and its copolymer, a polypropylene glycol, and its copolymer.
[Claim 4] Claim 1 characterized by carrying out coating of the anti-thrombus nature matter to the internal surface of said hollow fiber thru/or the hollow fiber for blood purification given in 3.
[Claim 5] Claim 1 characterized by said anti-thrombus nature matter being vitamin E thru/or the hollow fiber for blood purification given in 4.
[Claim 6] The hollow fiber mold artificial kidney which has the hollow fiber indicated by claim 1 thru/or 5.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the hollow fiber for blood purification and hollow fiber mold artificial kidney which are used for a blood purification therapy especially a hemodialysis therapy, and hemofiltration dialysis. In more detail, while preventing trespass of the endotoxin from a dialysing fluid side, it is related with the hollow fiber for blood purification and hollow fiber mold artificial kidney which suppressed adsorption of a platelet in the blood contact surface.
[0002]
[Description of the Prior Art] The various artificial kidneys which used the current hollow fiber for the renal failure therapy are used. In recent years, it is shown that clearance of with a molecular weight of 10,000 or more which made beta 2-microglobulin one index low-molecular-weight protein is effective in a therapy, and development of the blood purification film which has the fine hole which can pass low-molecular-weight protein has been performed briskly.

Furthermore, in order to remove low-molecular-weight protein positively, simultaneous hemofiltration dialysis which combined hemodialysis and hemofiltration is performed.
[0003] However, if the magnitude (pore size) of a membranous fine hole is expanded in order to remove low-molecular-weight protein since the dialysing fluid which flows an opposite hand on both sides of the film flows into a blood side in the case of the above-mentioned therapy, possibility that the endotoxin (endotoxin) contained in dialysing fluid will invade into a blood side increases, and we are anxious about causing side effects, such as generation of heat.
[0004] Endotoxin has a hydrophobic part, it is known that it will be easy to stick to a hydrophobic ingredient, and the endotoxin clearance filter using this principle is developed. JP,10-151196,A and JP,10-118472,A produce a hollow fiber only from a hydrophobic macromolecule, and are making endotoxin adsorb. In order to make lowering of the permeable ability by a hydrophobic macromolecule tending [furthermore] to adsorb the protein in blood improve, the hydrophilic macromolecule is made to adhere only to a hollow filament inner surface. In these applications, a film production undiluted solution is not made to mix a hydrophilic macromolecule, but hydrophilization processing of the internal surface is carried out after film production noting that hydrophobing of a film outside surface is impossible, if a hydrophilic macromolecule exists in a film production undiluted solution.
[0005] By the Prior art, pinpointing the suitable range was not shown by giving a hydrophilic macromolecule to the hollow fiber which consists of a hydrophobic macromolecule, taking adjustment with lowering of the adsorption capacity force of the endotoxin by that permeable ability improves and the hydrophilic property of a hollow fiber increasing.
[0006] Moreover, after adding a hydrophilic macromolecule to the film production undiluted solution of a hydrophobic macromolecule and producing a film to it, when decreasing the amount of the hydrophilic macromolecule of an outside surface by washing etc., the amount of hydrophilic macromolecules of the front face in contact with blood also decreases, and it is indicated by JP,6-296686,A that adhesion of a platelet etc. arises.
[0007]
[Problem(s) to be Solved by the Invention] The object of this invention is in the hollow fiber produced from the film production undiluted solution with which the hydrophilic macromolecule which solved the above-mentioned problem, and the hydrophobic macromolecule were mixed to offer the hollow fiber for blood purification and hollow fiber mold artificial kidney which adsorb endotoxin to an outside surface.
[0008] Furthermore, the object of this invention has a hydrophilic macromolecule in a hollow fiber in offering the hollow fiber for blood purification and hollow fiber mold artificial kidney to which a platelet is not made to stick few.
[0009]
[Means for Solving the Problem] Many above-mentioned objects are attained by the following hollow fibers for blood purification and hollow fiber mold artificial kidneys of this invention.
[0010] (1) The hollow fiber for blood purification characterized by the ratio of the hydrophilic macromolecule to the hydrophobic macromolecule in the outside surface of this hollow fiber being 5 - 25% in the hollow fiber manufactured from the film production undiluted solution which made the common solvent carry out dissolution mixing of a hydrophilic macromolecule and the hydrophobic macromolecule.
[0011] (2) The hollow fiber for blood purification given in (1) characterized by said hydrophobic macromolecule being polysulfone system resin.
[0012] (3) (1) characterized by being chosen out of the group which said hydrophilic giant

molecule becomes from a polyvinyl pyrrolidone, a polyethylene glycol and its copolymer, a polypropylene glycol, and its copolymer, or the hollow fiber for blood purification given in (2).
[0013] (4) The claim (1) characterized by carrying out coating of the anti-thrombus nature matter to the internal surface of said hollow fiber thru/or the hollow fiber for blood purification given in (3).
[0014] (5) (1) characterized by said anti-thrombus nature matter being vitamin E thru/or the hollow fiber for blood purification given in (4).
[0015] (6) The hollow fiber mold artificial kidney which has the hollow fiber indicated by the above (1) thru/or (5).
[0016]
[Embodiment of the Invention] This invention is explained to a detail below.
[0017] Polymethylmethacrylate, polystyrene, polysulfone, cellulose triacetate, a polycarbonate, polyarylate, etc. are mentioned, and the hydrophobic giant molecule which forms the hollow fiber for blood purification of this invention may be used combining these independence or two sorts or more. These hydrophobic macromolecules can prevent the trespass by the side of the blood of the endotoxin from a dialysing fluid side, when it has endotoxin adsorbent and it is used as an artificial kidney.
[0018] The hollow fiber for blood purification of this invention receives fixed washing processing in the film production undiluted solution after film production including a hydrophilic macromolecule, and remains in a hollow fiber. The hydrophilic giant molecule used for this invention contains the copolymer containing polymers, such as polyvinyl alcohol, a polyethylene glycol, a polypropylene glycol, a polyvinyl pyrrolidone, and polytetramethylene oxide, or these. A polyvinyl pyrrolidone is preferably desirable in respect of the ease of film production nature and aperture control. Moreover, 5 million dalton of desirable weight average molecular weight is 30,000 to 2 million dalton more preferably from 10,000. The aperture control for making it function as permeable membrane is easy.
[0019] 5 to 25% of the ratio to the hydrophobic macromolecule of the hydrophilic macromolecule by the side of the dialysing fluid which remains in the hollow fiber for blood purification of this invention (usually outside surface of a hollow fiber) is desirable. If it is this range, the endotoxin contained in dialysing fluid can be made to adsorb effectively. It is 5 to 20% more preferably. The ratio to the hydrophobic macromolecule of the hydrophilic macromolecule by the side of dialysing fluid says the rate of an abundance ratio of this hydrophilic macromolecule and this hydrophobic macromolecule measured with measuring methods, such as X-ray photoelectron spectroscopy (X-ray photoelectron spectroscopy, XPS), infrared spectroscopy, and a nuclear magnetic resonance method. For example, when a polyvinyl pyrrolidone (PVP) is chosen as polysulfone resin (PS) and a hydrophilic giant molecule as a hydrophobic giant molecule, the ratio of the total atomic weight of PS which exists in a hollow fiber front face, and each PVP can be computed and calculated by XPS from the sulfur (PS) and the element ratio of nitrogen (PVP) which are a characteristic element, and the repeat unit molecular weight of PS and PVP.
[0020] Moreover, the ratio of the hydrophilic macromolecule to the hydrophobic macromolecule of the whole hollow fiber of this invention has 1.0 to 6.0 desirable % of the weight. It is 2.0 to 5.0 % of the weight more preferably. Washing actuation must be performed superfluously and effectiveness is bad at below a lower limit. Moreover, above a upper limit, the ratio of a hydrophilic macromolecule will rise rapidly toward the interior of the film from a hollow fiber outside surface, the field to which endotoxin sticks decreases, and it is not desirable. The ratio of

the hydrophilic macromolecule of the whole hollow fiber has the approach of dissolving a hollow fiber in a solvent and analyzing by NMR etc., an approach by elemental analysis, etc. For example, when a polyvinyl pyrrolidone is used as polysulfone and a hydrophilic giant molecule as a hydrophobic giant molecule, a weight ratio can be calculated from the nitrogen and the sulphuric element ratio by elemental analysis, and the molecular weight of the repeat unit of each giant molecule.

[0021] When producing a hollow fiber, the wet spinning approach or the dryness-and-moisture type spinning approach used conventionally can be used. When performing these spinning approaches, said hydrophobic macromolecule and hydrophilic macromolecule are dissolved in these common solvents, and a film production undiluted solution is adjusted. As this common solvent, although solvents, such as N,N-dimethylacetamide, N.N-dimethylformamide, N-methyl pyrrolidone, and dimethyl sulfoxide, are highly suitable for solubility, it is not limited to these, and two or more sorts of solvents may be mixed, and you may use. It is the point of the ease of acquisition preferably and N,N-dimethylacetamide and N.N-dimethylformamide are used independently.

[0022] Moreover, in order to tune viscosity accommodation, aperture control, etc. finely to a film production undiluted solution, optimum dose addition of alcohol, a glycerol, the water, etc. may be carried out. The point of effluent processing to water is desirable, and 0.1 to 5 % of the weight is desirable to the above-mentioned fine adjustment in a film production undiluted solution.

[0023] When too low, film reinforcement is small, the concentration of the hydrophobic macromolecule in a film production undiluted solution must perform spinning activity and assembly operation carefully, and its effectiveness is bad. Moreover, if concentration is too high, the viscosity of a film production undiluted solution will rise, the film becomes precise, and the conditioning of the required aperture **** sake as an artificial kidney is difficult. When polysulfone is used as a hydrophobic macromolecule, the concentration in the film production undiluted solution of a desirable hydrophobic macromolecule is 15 to 19 % of the weight still more preferably 25% of the weight in 12 preferably 30% of the weight from 10. Since a desirable density range is changed with the class of hydrophobic macromolecule, molecular weight, etc. in a detail, it is not limited to this range.

[0024] If the concentration of the hydrophilic macromolecule in a film production undiluted solution is too low, good aperture control will become difficult, if too high, the viscosity of a film production undiluted solution will rise and spinning nature will get worse. When the polyvinyl pyrrolidone of weight-average-molecular-weight 45,000 Dalton is used as a hydrophilic giant molecule, the concentration in a desirable film production undiluted solution is 7 to 10 % of the weight more preferably 15% of the weight from 5. Concentration low when what has high molecular weight is used is sufficient, and high concentration is desirable when what has low molecular weight is used.

[0025] As internal liquid which carries out the regurgitation from the inner tube of a double pipe nozzle, the mixture of the above-mentioned common solvent and water is mainly used in the case of wet spinning or dryness-and-moisture type spinning. What mixed two or more sorts of above-mentioned common solvents for control of the coagulation rate of a film production undiluted solution, and other liquids may be mixed.

[0026] It is immersed in the coagulation bath to which the film production undiluted solution breathed out from the double pipe nozzle made water the subject. a film production undiluted solution -- a coagulation bath -- as a hollow fiber -- firmly -- form attachment ****. Then, if needed, it is immersed in a wash bath and rinses. PVP of an outside surface is washed, so that the

temperature of a wash bath is high. In order to adjust PVP of the outside surface of a hollow fiber into a desirable ratio, it is desirable to make temperature of a wash bath into 40 to 80 degrees C. It is desirable to wash especially at 50 to 70 degrees C. Since to move in the perimeter of a hollow fiber is [washing effectiveness] higher, the wash water of this wash bath circulates wash water, and may be used. Under the present circumstances, since the PVP concentration in wash water becomes high gradually and washing effectiveness falls during circulation, it is desirable to supply always new wash water. It is desirable that the amount of the new wash water supplied in 1 hour is 10 to 50 of a wash water total amount%.

[0027] The hollow fiber washed by the wash bath can wash PVP of a hollow fiber outside surface positively by performing rolling up and washing with the mixed solution of warm water, alcohol, alcohol, and water etc. further. Thus, the endotoxin adsorption capacity to an outside surface is obtained from 5 by considering as 5 to 20% preferably 25% in the rate of an abundance ratio of the hydrophilic macromolecule of the outside surface of the obtained hollow fiber. Water permeability decreases that the rate of an outside-surface abundance ratio of a hydrophilic macromolecule is less than 5%. If the rate of an outside-surface abundance ratio of a hydrophilic macromolecule exceeds 25%, the hydrophilic property of an outside surface will become high and the adsorption capacity of endotoxin will fall.

[0028] Moreover, as for the hollow fiber for blood purification of this invention, it is desirable to give the anti-thrombus nature matter in order to control platelet adhesion of the hollow filament internal surface in contact with blood. It is because the rate of an abundance ratio of the hydrophilic macromolecule of an internal surface also falls and a platelet becomes easy to adhere, when the rate of an abundance ratio of the hydrophilic macromolecule of a hollow fiber outside surface is made into 5 to 25%. With the anti-thrombus nature matter, fat soluble vitamins, such as long-chain unsaturated fatty acid, such as a polymeric material which has a hydrophilic part like a styrene-hydroxyethyl methacrylate copolymer and the polymer of the acrylic-acid system monomer which has a hydrophilic group (meta), and the acrylic-acid system monomer which has a hydrophobic group (meta), and a hydrophobic part, eicosapentaenoic acid, and docosa-hexaenoic acid, and vitamin E, are mentioned. The point that the stability over the ease and heat of processing is high to vitamin E is desirable. As vitamin E, the alpha-tocopherol, the beta-tocopherol, the gamma-tocopherol, delta-tocopherol, alpha-tocopherol acetate, alpha-tocopherol nicotinate, etc. are mentioned.

[0029] (Example 1) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 9 % of the weight (K-30) of polyvinyl pyrrolidones, and the 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. Internal liquid used 60 % of the weight of N.N-dimethylformamide, and the mixed liquor of 40 % of the weight of water.

[0030] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out by part for 1L/for 1 hour.

[0031] After shower washing, the hollow fiber was rolled round and it was made 10,000 bundles, and it processed underwater for 110 more degree-C 1 hour, and washed.

[0032] (Example 2) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 9 % of the weight (K-30) of polyvinyl pyrrolidones, and the 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was

adjusted. 0.1% of the weight of alpha-tocopherol acetate and 0.1% of the weight of a polyethylene-glycol-polypropylene-glycol copolymer (Pluronic F-68, Asahi Denka Kogyo K.K. make) were added and used for internal liquid to 60 % of the weight of N.N-dimethylformamide, and the mixed liquor of 40 % of the weight of water.

[0033] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out by part for 1L/for 1 hour.

[0034] After shower washing, the hollow fiber was rolled round and it was made 10,000 bundles, and it processed underwater for 110 more degree-C 1 hour, and washed.

[0035] (Example 1 of a comparison) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 9 % of the weight (K-30) of polyvinyl pyrrolidones, and the 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. internal liquid -- 60 % of the weight of N.N-dimethylformamide, and 40 % of the weight of water -- mixed liquor was carried out and it used.

[0036] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out for 10 minutes by part for 1L/.

[0037] (Example 2 of a comparison) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 1 % of the weight (K-30) of polyvinyl pyrrolidones, and the 80 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. internal liquid -- 60 % of the weight of N.N-dimethylformamide, and 40 % of the weight of water -- mixed liquor was carried out and it used.

[0038] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out by part for 1L/for 1 hour.

[0039] After shower washing, the hollow fiber was rolled round and it was made 10,000 bundles, and it processed underwater for 110 more degree-C 1 hour, and washed.

[0040] The rate of an abundance ratio of the polyvinyl pyrrolidone of the outside surface of the hollow fiber obtained in examples 1 and 2 and the examples 1 and 2 of a comparison was measured by XPS, the hollow fiber mold artificial kidney of 2 was produced 1.5m of effective film surface products using housing which has further the inside of a hollow fiber, a blood inlet port open for free passage, a blood outlet, and the dialysing fluid inlet port which is open for free passage the outside surface side of a hollow fiber and a dialysing fluid outlet, and permeable ability and endotoxin adsorption capacity were measured. A measurement result is shown in a table 1.

[0041] Using the above-mentioned hollow fiber mold artificial kidney, measurement of permeable ability returned Milli Q water by rate-of-flow 200 ml/min inside the hollow fiber, from the outside surface of a hollow fiber, was filtered by rate-of-flow 15 ml/min, and measured and computed the pressure differential between film at that time.

[0042] Measurement of the adsorption capacity of endotoxin was performed using the above-

mentioned hollow fiber mold artificial kidney as follows. The dialysing fluid which sent the dialysing fluid of endotoxin concentration 800 EU/L by rate-of-flow 30 ml/min from the dialysing fluid inlet port, controlled the flow from a dialysing fluid outlet to 5 ml/min using the pump, filtered the dialysing fluid which contains endotoxin from the outside surface side of a hollow fiber to the inside positively for 4 hours, and was filtered from the outside of a hollow fiber in the inside of a hollow fiber was stored, and the endotoxin concentration of this reservoir liquid was measured. Test fluid was not recycled but circulated only to the one direction.
[0043]
[A table 1]

	膜全体のPVP比率(%)	PVP外表面比率(%)	透水性能(ml/mmHg·hr)	エンドトキシン濃度(EU／L)
実施例1	2．8	17	490	検出限界以下
実施例2	2．3	14	470	検出限界以下
比較例1	6．7	30	460	8
比較例2	0．8	3	20	検出限界以下

検出限界：1EU／L

[0044] As a table 1, examples 1 and 2 have permeable ability equivalent to the example 1 of a comparison, and have the adsorption capacity of endotoxin. On the other hand, as for the example 1 of a comparison, endotoxin was detected by reverse filtration of dialysing fluid of 4 hours to the blood side. Moreover, although the endotoxin by the side of blood was not detected for the example 2 of a comparison, permeable ability decreased prominent.
[0045] (Example 3) Polymer concentration was diluted with the methanol for 30% methyl-isobutyl-ketone solution of polymer concentration of the random copolymer (polymer 1) of hydroxyethyl methacrylate, methyl methacrylate, and butyl methacrylate, and the block copolymer (the ratio of polymers 1 and 2 is the weight ratio 50:50 and a mean molecular weight 35,000) of polyperfluoro alkyl methacrylate (polymer 2) to 0.7%. After dipping this solution in PS film inner surface of an example 1, the solvent was removed by 50-degree C desiccation, and the polymer was coated on PS film.
[0046] The permeable ability of the artificial kidney of 2 was 320 ml/mmHg-hr 1.5m of effective film surface products in the obtained hollow fiber.
[0047] (Aging of a platelet count) The mini module of 2 was produced 300cm of film surface products using the hollow fiber obtained in the example 1, the example 2, and the example 3.
[0048] Twice many Nembutal eating-raw-food [as this] diluent 1 ml/kg was injected intravenously and anesthetized using the rabbit (weight of 2.7-3.3kg). The rabbit was fixed to standing ways, the blood vessel of a neck condition pulse was secured, and it circulated for 2 hours, without connecting a circuit and a mini module and using an anticoagulant by blood stream QB=10 ml/min. Blood collecting was performed from the artery side blood collecting port of a mini module, and aging of a platelet count was measured. In addition, the rate of change of a platelet was amended with the hematocrit value (bottom type).
[0049]
[Equation 1]

$$\text{血球変化率} = \frac{PL_t \times Ht_0}{PL_0 \times Ht_t} \times 100\%$$

PL_0：循環前の血球数、Ht_0：循環前のヘマトクリット値

PL_t：循環t時間の血球数、Ht_t：循環t時間のヘマトクリット値

[0050] A result is shown in a table 2.
[0051]
[A table 2]

時間(分)	実施例1	実施例2	実施例3
0	100	100	100
5	90.1	93.5	89.7
10	89.1	90.8	86.0
15	83.8	90.4	84.6
20	81.9	87.2	85.7
25	79.9	86.7	84.3
30	75.1	85.5	84.9
45	65.5	84.0	83.3
60	61.6	80.9	81.6
120	57.5	84.8	81.3

[0052] (Measurement of erythrocyte membrane MDA) The following actuation was performed using the mini module of the example 1 of 2, and an example 2 600cm of film surface products.
[0053] First, the priming of the 50ml of the sterilized mini modules was carried out by eating raw food, the mini module was filled up with 10U/ml heparinized blood, and it incubated at 37 degrees C for 6 hours. Then, blood was collected from the mini module and the number of red cell was counted by the corpuscle computer (Sysmex SE9000 and TOA Medical Electronics Co., Ltd.) (red blood cell count). Moreover, the erythrocyte which removed plasma according to plasma skimming (3,000rpm, 15min, 4 degrees C), and precipitated to 10mM PBS(pH8.0)5.4ml in 1.8ml (finishing [a red blood cell count]) of blood collected from the mini module was made to suspend, centrifugal separation (3,000rpm, 15min, 4 degrees C) was carried out, and PBS of supernatant liquid was removed and washed. After performing this washing actuation a total of 3 times, PBS of supernatant liquid was removed, 5mMPBS(pH8.0)5.4ml was added, and the hemolysis of the erythrocyte was carried out.
[0054] Centrifugal separation (10,000rpm, 15min, 4 degrees C) of the above-mentioned sample which carried out the hemolysis is carried out, PBS of supernatant liquid is removed, and the hemolysis of the 2.5mMPBS(s)(pH8.0)5.4ml is mixed and carried out to an erythrocyte. Furthermore centrifugal separation (10,000rpm, 15min, 4 degrees C) was carried out, PBS of supernatant liquid was removed, the hemolysis of the 1.25mMPBS(s)(pH8.0)5.4ml was mixed and carried out to the erythrocyte, and centrifugal separation (10,000rpm, 15min, 4 degrees C) was carried out. The hemolysis in 1.25mMPBS(s), centrifugal separation, and washing actuation are repeated a total of 5 times. After removing PBS of supernatant liquid finally, the whole quantity was doubled with 2ml by 1.25mMPBS.
[0055] MDA (malondialdehyde) was measured for the erythrocyte membrane obtained by the above-mentioned preparation by the TBA method as a sample (peroxylipid Test Wako: Wako Pure Chem industrial company make). Operating instructions are shown below.

[0056] A result is shown in a table 3.
[0057]
[A table 3]
赤血球過酸化脂質（n=5）

	MDA nmol／10^{10}RBC
PRE	3．507
実施1	6．701
実施2	5．558

[0058] By coating a hollow fiber inner surface side with the anti-thrombus nature matter shows that reduction in a platelet can be controlled. Moreover, when vitamin E is used, it turns out that peroxidation of an erythrocyte membrane lipid can be controlled.
[0059]
[Effect of the Invention] This invention can obtain the hollow fiber for blood purification and hollow fiber mold artificial kidney which adsorb endotoxin to an outside surface in the hollow fiber produced from the film production undiluted solution with which the hydrophilic macromolecule and the hydrophobic macromolecule were mixed as explained above.
[0060] Furthermore, this invention can obtain the hollow fiber for blood purification and hollow fiber mold artificial kidney to which the hydrophilic macromolecule in a hollow fiber does not make a platelet stick few.

TECHNICAL FIELD

[Field of the Invention] This invention relates to the hollow fiber for blood purification and hollow fiber mold artificial kidney which are used for a blood purification therapy especially a hemodialysis therapy, and hemofiltration dialysis. In more detail, while preventing trespass of the endotoxin from a dialysing fluid side, it is related with the hollow fiber for blood purification and hollow fiber mold artificial kidney which suppressed adsorption of a platelet in the blood contact surface.

PRIOR ART

[Description of the Prior Art] The various artificial kidneys which used the current hollow fiber for the renal failure therapy are used. In recent years, it is shown that clearance of with a molecular weight of 10,000 or more which made beta 2-microglobulin one index low-molecular-weight protein is effective in a therapy, and development of the blood purification film which has the fine hole which can pass low-molecular-weight protein has been performed briskly. Furthermore, in order to remove low-molecular-weight protein positively, simultaneous hemofiltration dialysis which combined hemodialysis and hemofiltration is performed.
[0003] However, if the magnitude (pore size) of a membranous fine hole is expanded in order to remove low-molecular-weight protein since the dialysing fluid which flows an opposite hand on both sides of the film flows into a blood side in the case of the above-mentioned therapy,

possibility that the endotoxin (endotoxin) contained in dialysing fluid will invade into a blood side increases, and we are anxious about causing side effects, such as generation of heat.
[0004] Endotoxin has a hydrophobic part, it is known that it will be easy to stick to a hydrophobic ingredient, and the endotoxin clearance filter using this principle is developed. JP,10-151196,A and JP,10-118472,A produce a hollow fiber only from a hydrophobic macromolecule, and are making endotoxin adsorb. In order to make lowering of the permeable ability by a hydrophobic macromolecule tending [furthermore] to adsorb the protein in blood improve, the hydrophilic macromolecule is made to adhere only to a hollow filament inner surface. In these applications, a film production undiluted solution is not made to mix a hydrophilic macromolecule, but hydrophilization processing of the internal surface is carried out after film production noting that hydrophobing of a film outside surface is impossible, if a hydrophilic macromolecule exists in a film production undiluted solution.
[0005] By the Prior art, pinpointing the suitable range was not shown by giving a hydrophilic macromolecule to the hollow fiber which consists of a hydrophobic macromolecule, taking adjustment with lowering of the adsorption capacity force of the endotoxin by that permeable ability improves and the hydrophilic property of a hollow fiber increasing.
[0006] Moreover, after adding a hydrophilic macromolecule to the film production undiluted solution of a hydrophobic macromolecule and producing a film to it, when decreasing the amount of the hydrophilic macromolecule of an outside surface by washing etc., the amount of hydrophilic macromolecules of the front face in contact with blood also decreases, and it is indicated by JP,6-296686,A that adhesion of a platelet etc. arises.

EFFECT OF THE INVENTION

[Effect of the Invention] This invention can obtain the hollow fiber for blood purification and hollow fiber mold artificial kidney which adsorb endotoxin to an outside surface in the hollow fiber produced from the film production undiluted solution with which the hydrophilic macromolecule and the hydrophobic macromolecule were mixed as explained above.
[0060] Furthermore, this invention can obtain the hollow fiber for blood purification and hollow fiber mold artificial kidney to which the hydrophilic macromolecule in a hollow fiber does not make a platelet stick few.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] The object of this invention is in the hollow fiber produced from the film production undiluted solution with which the hydrophilic macromolecule which solved the above-mentioned problem, and the hydrophobic macromolecule were mixed to offer the hollow fiber for blood purification and hollow fiber mold artificial kidney which adsorb endotoxin to an outside surface.
[0008] Furthermore, the object of this invention has a hydrophilic macromolecule in a hollow fiber in offering the hollow fiber for blood purification and hollow fiber mold artificial kidney to which a platelet is not made to stick few.

MEANS

[Means for Solving the Problem] Many above-mentioned objects are attained by the following hollow fibers for blood purification and hollow fiber mold artificial kidneys of this invention.
[0010] (1) The hollow fiber for blood purification characterized by the ratio of the hydrophilic macromolecule to the hydrophobic macromolecule in the outside surface of this hollow fiber being 5 - 25% in the hollow fiber manufactured from the film production undiluted solution which made the common solvent carry out dissolution mixing of a hydrophilic macromolecule and the hydrophobic macromolecule.
[0011] (2) The hollow fiber for blood purification given in (1) characterized by said hydrophobic macromolecule being polysulfone system resin.
[0012] (3) (1) characterized by being chosen out of the group which said hydrophilic giant molecule becomes from a polyvinyl pyrrolidone, a polyethylene glycol and its copolymer, a polypropylene glycol, and its copolymer, or the hollow fiber for blood purification given in (2).
[0013] (4) The claim (1) characterized by carrying out coating of the anti-thrombus nature matter to the internal surface of said hollow fiber thru/or the hollow fiber for blood purification given in (3).
[0014] (5) (1) characterized by said anti-thrombus nature matter being vitamin E thru/or the hollow fiber for blood purification given in (4).
[0015] (6) The hollow fiber mold artificial kidney which has the hollow fiber indicated by the above (1) thru/or (5).
[0016]
[Embodiment of the Invention] This invention is explained to a detail below.
[0017] Polymethylmethacrylate, polystyrene, polysulfone, cellulose triacetate, a polycarbonate, polyarylate, etc. are mentioned, and the hydrophobic giant molecule which forms the hollow fiber for blood purification of this invention may be used combining these independence or two sorts or more. These hydrophobic macromolecules can prevent the trespass by the side of the blood of the endotoxin from a dialysing fluid side, when it has endotoxin adsorbent and it is used as an artificial kidney.
[0018] The hollow fiber for blood purification of this invention receives fixed washing processing in the film production undiluted solution after film production including a hydrophilic macromolecule, and remains in a hollow fiber. The hydrophilic giant molecule used for this invention contains the copolymer containing polymers, such as polyvinyl alcohol, a polyethylene glycol, a polypropylene glycol, a polyvinyl pyrrolidone, and polytetramethylene oxide, or these. A polyvinyl pyrrolidone is preferably desirable in respect of the ease of film production nature and aperture control. Moreover, 5 million dalton of desirable weight average molecular weight is 30,000 to 2 million dalton more preferably from 10,000. The aperture control for making it function as permeable membrane is easy.
[0019] 5 to 25% of the ratio to the hydrophobic macromolecule of the hydrophilic macromolecule by the side of the dialysing fluid which remains in the hollow fiber for blood purification of this invention (usually outside surface of a hollow fiber) is desirable. If it is this range, the endotoxin contained in dialysing fluid can be made to adsorb effectively. It is 5 to 20% more preferably. The ratio to the hydrophobic macromolecule of the hydrophilic macromolecule by the side of dialysing fluid says the rate of an abundance ratio of this hydrophilic macromolecule and this hydrophobic macromolecule measured with measuring

methods, such as X-ray photoelectron spectroscopy (X-ray photoelectron spectroscopy, XPS), infrared spectroscopy, and a nuclear magnetic resonance method. For example, when a polyvinyl pyrrolidone (PVP) is chosen as polysulfone resin (PS) and a hydrophilic giant molecule as a hydrophobic giant molecule, the ratio of the total atomic weight of PS which exists in a hollow fiber front face, and each PVP can be computed and calculated by XPS from the sulfur (PS) and the element ratio of nitrogen (PVP) which are a characteristic element, and the repeat unit molecular weight of PS and PVP.

[0020] Moreover, the ratio of the hydrophilic macromolecule to the hydrophobic macromolecule of the whole hollow fiber of this invention has 1.0 to 6.0 desirable % of the weight. It is 2.0 to 5.0 % of the weight more preferably. Washing actuation must be performed superfluously and effectiveness is bad at below a lower limit. Moreover, above a upper limit, the ratio of a hydrophilic macromolecule will rise rapidly toward the interior of the film from a hollow fiber outside surface, the field to which endotoxin sticks decreases, and it is not desirable. The ratio of the hydrophilic macromolecule of the whole hollow fiber has the approach of dissolving a hollow fiber in a solvent and analyzing by NMR etc., an approach by elemental analysis, etc. For example, when a polyvinyl pyrrolidone is used as polysulfone and a hydrophilic giant molecule as a hydrophobic giant molecule, a weight ratio can be calculated from the nitrogen and the sulphuric element ratio by elemental analysis, and the molecular weight of the repeat unit of each giant molecule.

[0021] When producing a hollow fiber, the wet spinning approach or the dryness-and-moisture type spinning approach used conventionally can be used. When performing these spinning approaches, said hydrophobic macromolecule and hydrophilic macromolecule are dissolved in these common solvents, and a film production undiluted solution is adjusted. As this common solvent, although solvents, such as N,N-dimethylacetamide, N.N-dimethylformamide, N-methyl pyrrolidone, and dimethyl sulfoxide, are highly suitable for solubility, it is not limited to these, and two or more sorts of solvents may be mixed, and you may use. It is the point of the ease of acquisition preferably and N,N-dimethylacetamide and N.N-dimethylformamide are used independently.

[0022] Moreover, in order to tune viscosity accommodation, aperture control, etc. finely to a film production undiluted solution, optimum dose addition of alcohol, a glycerol, the water, etc. may be carried out. The point of effluent processing to water is desirable, and 0.1 to 5 % of the weight is desirable to the above-mentioned fine adjustment in a film production undiluted solution.

[0023] When too low, film reinforcement is small, the concentration of the hydrophobic macromolecule in a film production undiluted solution must perform spinning activity and assembly operation carefully, and its effectiveness is bad. Moreover, if concentration is too high, the viscosity of a film production undiluted solution will rise, the film becomes precise, and the conditioning of the required aperture **** sake as an artificial kidney is difficult. When polysulfone is used as a hydrophobic macromolecule, the concentration in the film production undiluted solution of a desirable hydrophobic macromolecule is 15 to 19 % of the weight still more preferably 25% of the weight in 12 preferably 30% of the weight from 10. Since a desirable density range is changed with the class of hydrophobic macromolecule, molecular weight, etc. in a detail, it is not limited to this range.

[0024] If the concentration of the hydrophilic macromolecule in a film production undiluted solution is too low, good aperture control will become difficult, if too high, the viscosity of a film production undiluted solution will rise and spinning nature will get worse. When the polyvinyl pyrrolidone of weight-average-molecular-weight 45,000 Dalton is used as a

hydrophilic giant molecule, the concentration in a desirable film production undiluted solution is 7 to 10 % of the weight more preferably 15% of the weight from 5. Concentration low when what has high molecular weight is used is sufficient, and high concentration is desirable when what has low molecular weight is used.

[0025] As internal liquid which carries out the regurgitation from the inner tube of a double pipe nozzle, the mixture of the above-mentioned common solvent and water is mainly used in the case of wet spinning or dryness-and-moisture type spinning. What mixed two or more sorts of above-mentioned common solvents for control of the coagulation rate of a film production undiluted solution, and other liquids may be mixed.

[0026] It is immersed in the coagulation bath to which the film production undiluted solution breathed out from the double pipe nozzle made water the subject. a film production undiluted solution -- a coagulation bath -- as a hollow fiber -- firmly -- form attachment ****. Then, if needed, it is immersed in a wash bath and rinses. PVP of an outside surface is washed, so that the temperature of a wash bath is high. In order to adjust PVP of the outside surface of a hollow fiber into a desirable ratio, it is desirable to make temperature of a wash bath into 40 to 80 degrees C. It is desirable to wash especially at 50 to 70 degrees C. Since to move in the perimeter of a hollow fiber is [washing effectiveness] higher, the wash water of this wash bath circulates wash water, and may be used. Under the present circumstances, since the PVP concentration in wash water becomes high gradually and washing effectiveness falls during circulation, it is desirable to supply always new wash water. It is desirable that the amount of the new wash water supplied in 1 hour is 10 to 50 of a wash water total amount%.

[0027] The hollow fiber washed by the wash bath can wash PVP of a hollow fiber outside surface positively by performing rolling up and washing with the mixed solution of warm water, alcohol, alcohol, and water etc. further. Thus, the endotoxin adsorption capacity to an outside surface is obtained from 5 by considering as 5 to 20% preferably 25% in the rate of an abundance ratio of the hydrophilic macromolecule of the outside surface of the obtained hollow fiber. Water permeability decreases that the rate of an outside-surface abundance ratio of a hydrophilic macromolecule is less than 5%. If the rate of an outside-surface abundance ratio of a hydrophilic macromolecule exceeds 25%, the hydrophilic property of an outside surface will become high and the adsorption capacity of endotoxin will fall.

[0028] Moreover, as for the hollow fiber for blood purification of this invention, it is desirable to give the anti-thrombus nature matter in order to control platelet adhesion of the hollow filament internal surface in contact with blood. It is because the rate of an abundance ratio of the hydrophilic macromolecule of an internal surface also falls and a platelet becomes easy to adhere, when the rate of an abundance ratio of the hydrophilic macromolecule of a hollow fiber outside surface is made into 5 to 25%. With the anti-thrombus nature matter, fat soluble vitamins, such as long-chain unsaturated fatty acid, such as a polymeric material which has a hydrophilic part like a styrene-hydroxyethyl methacrylate copolymer and the polymer of the acrylic-acid system monomer which has a hydrophilic group (meta), and the acrylic-acid system monomer which has a hydrophobic group (meta), and a hydrophobic part, eicosapentaenoic acid, and docosa-hexaenoic acid, and vitamin E, are mentioned. The point that the stability over the ease and heat of processing is high to vitamin E is desirable. As vitamin E, the alpha-tocopherol, the beta-tocopherol, the gamma-tocopherol, delta-tocopherol, alpha-tocopherol acetate, alpha-tocopherol nicotinate, etc. are mentioned.

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the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. Internal liquid used 60 % of the weight of N.N-dimethylformamide, and the mixed liquor of 40 % of the weight of water.
[0030] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out by part for 1L/for 1 hour.
[0031] After shower washing, the hollow fiber was rolled round and it was made 10,000 bundles, and it processed underwater for 110 more degree-C 1 hour, and washed.
[0032] (Example 2) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 9 % of the weight (K-30) of polyvinyl pyrrolidones, and the 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. 0.1% of the weight of alpha-tocopherol acetate and 0.1% of the weight of a polyethylene-glycol-polypropylene-glycol copolymer (Pluronic F-68, Asahi Denka Kogyo K.K. make) were added and used for internal liquid to 60 % of the weight of N.N-dimethylformamide, and the mixed liquor of 40 % of the weight of water.
[0033] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out by part for 1L/for 1 hour.
[0034] After shower washing, the hollow fiber was rolled round and it was made 10,000 bundles, and it processed underwater for 110 more degree-C 1 hour, and washed.
[0035] (Example 1 of a comparison) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 9 % of the weight (K-30) of polyvinyl pyrrolidones, and the 72 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. internal liquid -- 60 % of the weight of N.N-dimethylformamide, and 40 % of the weight of water -- mixed liquor was carried out and it used.
[0036] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out for 10 minutes by part for 1L/.
[0037] (Example 2 of a comparison) The homogeneity dissolution of 19 % of the weight (P-1700) of polysulfones, 1 % of the weight (K-30) of polyvinyl pyrrolidones, and the 80 % of the weight of the N.N-dimethylformamide was carried out, and the film production undiluted solution was adjusted. internal liquid -- 60 % of the weight of N.N-dimethylformamide, and 40 % of the weight of water -- mixed liquor was carried out and it used.
[0038] The coagulation bath with which discharge and water were simultaneously filled in air from the outer tube and inner tube of a double tubing regurgitation nozzle in an above-mentioned film production undiluted solution and internal liquid, respectively was passed. After passing a coagulation bath, shower washing of the 60-degree C warm water was carried out by part for 1L/for 1 hour.
[0039] After shower washing, the hollow fiber was rolled round and it was made 10,000 bundles, and it processed underwater for 110 more degree-C 1 hour, and washed.

[0040] The rate of an abundance ratio of the polyvinyl pyrrolidone of the outside surface of the hollow fiber obtained in examples 1 and 2 and the examples 1 and 2 of a comparison was measured by XPS, the hollow fiber mold artificial kidney of 2 was produced 1.5m of effective film surface products using housing which has further the inside of a hollow fiber, a blood inlet port open for free passage, a blood outlet, and the dialysing fluid inlet port which is open for free passage the outside surface side of a hollow fiber and a dialysing fluid outlet, and permeable ability and endotoxin adsorption capacity were measured. A measurement result is shown in a table 1.
[0041] Using the above-mentioned hollow fiber mold artificial kidney, measurement of permeable ability returned Milli Q water by rate-of-flow 200 ml/min inside the hollow fiber, from the outside surface of a hollow fiber, was filtered by rate-of-flow 15 ml/min, and measured and computed the pressure differential between film at that time.
[0042] Measurement of the adsorption capacity of endotoxin was performed using the above-mentioned hollow fiber mold artificial kidney as follows. The dialysing fluid which sent the dialysing fluid of endotoxin concentration 800 EU/L by rate-of-flow 30 ml/min from the dialysing fluid inlet port, controlled the flow from a dialysing fluid outlet to 5 ml/min using the pump, filtered the dialysing fluid which contains endotoxin from the outside surface side of a hollow fiber to the inside positively for 4 hours, and was filtered from the outside of a hollow fiber in the inside of a hollow fiber was stored, and the endotoxin concentration of this reservoir liquid was measured. Test fluid was not recycled but circulated only to the one direction.
[0043]
[A table 1]

	膜全体のＰＶＰ比率（%）	ＰＶＰ外表面比率（%）	透水性能（ml/mmHg・hr）	エンドトキシン濃度（ＥＵ／Ｌ）
実施例１	２．８	１７	４９０	検出限界以下
実施例２	２．３	１４	４７０	検出限界以下
比較例１	６．７	３０	４６０	8
比較例２	０．８	3	２０	検出限界以下

検出限界：１ＥＵ／Ｌ

[0044] As a table 1, examples 1 and 2 have permeable ability equivalent to the example 1 of a comparison, and have the adsorption capacity of endotoxin. On the other hand, as for the example 1 of a comparison, endotoxin was detected by reverse filtration of dialysing fluid of 4 hours to the blood side. Moreover, although the endotoxin by the side of blood was not detected for the example 2 of a comparison, permeable ability decreased prominent.
[0045] (Example 3) Polymer concentration was diluted with the methanol for 30% methyl-isobutyl-ketone solution of polymer concentration of the random copolymer (polymer 1) of hydroxyethyl methacrylate, methyl methacrylate, and butyl methacrylate, and the block copolymer (the ratio of polymers 1 and 2 is the weight ratio 50:50 and a mean molecular weight 35,000) of polyperfluoro alkyl methacrylate (polymer 2) to 0.7%. After dipping this solution in PS film inner surface of an example 1, the solvent was removed by 50-degree C desiccation, and the polymer was coated on PS film.
[0046] The permeable ability of the artificial kidney of 2 was 320 ml/mmHg-hr 1.5m of effective

film surface products in the obtained hollow fiber.
[0047] (Aging of a platelet count) The mini module of 2 was produced 300cm of film surface products using the hollow fiber obtained in the example 1, the example 2, and the example 3.
[0048] Twice many Nembutal eating-raw-food [as this] diluent 1 ml/kg was injected intravenously and anesthetized using the rabbit (weight of 2.7-3.3kg). The rabbit was fixed to standing ways, the blood vessel of a neck condition pulse was secured, and it circulated for 2 hours, without connecting a circuit and a mini module and using an anticoagulant by blood stream QB=10 ml/min. Blood collecting was performed from the artery side blood collecting port of a mini module, and aging of a platelet count was measured. In addition, the rate of change of a platelet was amended with the hematocrit value (bottom type).
[0049]
[Equation 1]

$$\text{血球変化率} = \frac{PL_t \times Ht_0}{PL_0 \times Ht_t} \times 100\%$$

PL_0：循環前の血球数、Ht_0：循環前のヘマトクリット値

PL_t：循環 t 時間の血球数、Ht_t：循環 t 時間のヘマトクリット値

[0050] A result is shown in a table 2.
[0051]
[A table 2]

時間(分)	実施例1	実施例2	実施例3
0	100	100	100
5	90.1	93.5	89.7
10	89.1	90.8	86.0
15	83.8	90.4	84.6
20	81.9	87.2	85.7
25	79.9	86.7	84.3
30	75.1	85.5	84.9
45	65.5	84.0	83.3
60	61.6	80.9	81.6
120	57.5	84.8	81.3

[0052] (Measurement of erythrocyte membrane MDA) The following actuation was performed using the mini module of the example 1 of 2, and an example 2 600cm of film surface products.
[0053] First, the priming of the 50ml of the sterilized mini modules was carried out by eating raw food, the mini module was filled up with 10U/ml heparinized blood, and it incubated at 37 degrees C for 6 hours. Then, blood was collected from the mini module and the number of red cell was counted by the corpuscle computer (Sysmex SE9000 and TOA Medical Electronics Co., Ltd.) (red blood cell count). Moreover, the erythrocyte which removed plasma according to plasma skimming (3,000rpm, 15min, 4 degrees C), and precipitated to 10mM PBS(pH8.0)5.4ml in 1.8ml (finishing [a red blood cell count]) of blood collected from the mini module was made to suspend, centrifugal separation (3,000rpm, 15min, 4 degrees C) was carried out, and PBS of supernatant liquid was removed and washed. After performing this washing actuation a total of 3 times, PBS of supernatant liquid was removed, 5mMPBS(pH8.0)5.4ml was added, and the hemolysis of the erythrocyte was carried out.

[0054] Centrifugal separation (10,000rpm, 15min, 4 degrees C) of the above-mentioned sample which carried out the hemolysis is carried out, PBS of supernatant liquid is removed, and the hemolysis of the 2.5mMPBS(s)(pH8.0)5.4ml is mixed and carried out to an erythrocyte. Furthermore centrifugal separation (10,000rpm, 15min, 4 degrees C) was carried out, PBS of supernatant liquid was removed, the hemolysis of the 1.25mMPBS(s)(pH8.0)5.4ml was mixed and carried out to the erythrocyte, and centrifugal separation (10,000rpm, 15min, 4 degrees C) was carried out. The hemolysis in 1.25mMPBS(s), centrifugal separation, and washing actuation are repeated a total of 5 times. After removing PBS of supernatant liquid finally, the whole quantity was doubled with 2ml by 1.25mMPBS.
[0055] MDA (malondialdehyde) was measured for the erythrocyte membrane obtained by the above-mentioned preparation by the TBA method as a sample (peroxylipid Test Wako: Wako Pure Chem industrial company make). Operating instructions are shown below.
[0056] A result is shown in a table 3.
[0057]
[A table 3]

赤血球過酸化脂質（n=5）

	MDA nmol／10^{10}RBC
PRE	3．507
実施1	6．701
実施2	5．558

[0058] By coating a hollow fiber inner surface side with the anti-thrombus nature matter shows that reduction in a platelet can be controlled. Moreover, when vitamin E is used, it turns out that peroxidation of an erythrocyte membrane lipid can be controlled.

[Translation done.]